TENT COOPERATION TRE

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 October 2000 (06.10.00)	
International application No. PCT/CA99/00005	**Applicant's or agent's file reference** 10242-16
International filing date (day/month/year) 13 January 1999 (13.01.99)	**Priority date** (day/month/year) 13 January 1998 (13.01.98)
Applicant UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 August 1999 (13.08.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Roberto HIDALGO

Telephone No.: (41-22) 338.83.38

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TENT COOPERATION TRE

From the INTERNATIONAL BUREAU

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Date of mailing (day/month/year) 14 October 1999 (14.10.99)	
International application No. PCT/CA99/00005	**Applicant's or agent's file reference** 10242-16
International filing date (day/month/year) 13 January 1999 (13.01.99)	**Priority date** (day/month/year) 13 January 1998 (13.01.98)
Applicant WARRINGTON, R., C. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 August 1999 (13.08.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2898564

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
10242-16		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00005	13/01/1999	13/01/1998
International Patent Classification (IPC) or national classification and IPC A61K33/24		
Applicant UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/08/1999	14.04.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Taylor, G.M. Telephone No. +49 89 2399 8406

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00005

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-19 as originally filed

Claims, No.:

1-51 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-51.

because:

☒ the said international application, or the said claims Nos. 1-51 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2-4,35-37 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,5-34,38-51
	No:	Claims	
Inventive step (IS)	Yes:	Claims	6-18,23-33,39-51
	No:	Claims	1,5,19-22,34,38
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section I

1. This IPER is issued as if the amendments filed had not been made, since they are considered to go beyond the disclosure as originally filed (Rule 70.2 PCT). In particular, the extension of the claims to <u>any</u> compound according to Formula I is considered as an extension of subject-matter because the application as filed makes reference throughout to propyargylamines, i.e. compounds of formula I in which z=1. Although formula I discloses other types of compound possessing an acetylenic group, the general teaching of the application is consistent in its reference to propyrgylamines. See, for example: p.1, lines 6-7; p.5, lines 7-16; p.5, line 17 to p.8, line 10; examples. As a consequence, an extension of the claims to include other compounds falling within formula I cannot be seen as an obvious correction, since the overwhelming evidence - including the examples - points to the use of propargylamines.

Section III

2. Claims 1-51 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3. Claims 2-4 and 35-37 define the subject-matter in terms of a result to be achieved and not a technical feature as required by Rule 6.3(a) PCT. Thus, the following definitions:

> "wherein the propargylamine increases the sensitivity of a tumour to the antineoplastic drug" (claim 2, 3, 35 and 36); and
>
> "wherein the propargylamine protects normal cells from the cytotoxic effects of the antineoplastic drug" (claims 4 and 37)

merely repeat the underlying technical problem of the application (see description: p.1, lines 4-11; p.3, lines 8-19; and p.5, lines 7-16).

This Authority considers that such a definition is unclear and inadequately supported by the description (Art. 5 and 6 PCT) because those specific

propargylamines suitable for this purpose are not disclosed. Thus, no meaningful opinion can be formed on the subject-matter of claims 2-4 and 35-37 (Art. 34(4)(a)(i) PCT).

Section V

4. In view of the prior art cited in the International Search Report, claims 1, 5-34 and 38-51 would appear to meet the requirements of Art. 33(2) PCT.

5. Claims 1, 5, 19-22, 34 and 38 do not appear to meet the requirements of Art. 33(3) PCT.

It is not possible that all propargylamines are suitable for such a purpose. For example, propargylamine itself is a highly toxic irritant and would not appear suitable for use in pharmaceuticals. Thus, the underlying technical problem is not solved over the whole scope of the said claims (Art. 6 and 33 PCT).

Furthermore, certain propargylamines are known from **US-A-4 460 599 (D1)** as anti-tumour agents. See, for example, claim 2, col.16, lines 54-57. It would therefore appear obvious to provide combinations of anti-tumour agents containing a known anti-tumour agent and those according to D1 which are propargylamines (Art. 33 PCT).

It would therefore appear that the application should be restricted to those compounds for which an effect has been shown. See also Item 6 below.

6. For the assessment of the present claims 1-51 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

7. Claims 6, 7, 10, 23, 24, 27, 39, 40 and 43 are unclear because the compounds

are only "propargylamines" when z=1. When z=0, these compounds are ethynylamines; when z=2-5, these compounds are propargylalkylamines. The term 'propargyl' refers to the radical CH[SPEC060e]C-CH_2-, and a propargylamine would have the structure RC[SPEC060e]C-CR'_2-$NR"_2$.

It is noted, however, that there appears to be no support in the description for restriction of this value to z=1 (cf. Art. 19(2) and 34(2)(b) PCT).

8. Claims 6, 23 and 39 do not meet the requirements of Art. 6 PCT since the meaning of the term 'lower alkyl' is unclear in that it does not have a generally-accepted meaning with respect to the maximum number of carbon atoms.

9. Claim 34 is unclear (Art. 6 PCT) because it is unclear how such a method would work in a case where the animal is not receiving an anti-neoplastic drug (the claim is not restricted to animals receiving such drugs).

10. The number of independent claims would appear to be unreasonable (Rules 6.1(a) and 6.4 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
10242-16		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00005	13/01/1999	13/01/1998

Applicant

UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

COMPOSITION CONTAINING PROPARGYLAMINE FOR ENHANCING CANCER THERAPY

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]national application No.
PCT/CA 99/00005

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 34-51
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 34-51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

[redacted]RNATIONAL SEARCH REPORT

[redacted]onal Application No
[redacted]T/CA 99/00005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/24 A61K31/675 A61K31/505 A61K31/70 A61K31/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 460 599 A (REMERS WILLIAM A) 17 July 1984 see claims	1
A	US 5 169 868 A (DAVIS BRUCE A ET AL) 8 December 1992 cited in the application see claims	1-51

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 1999	01/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

1

[redacted]NATIONAL SEARCH REPORT

[redacted]formation on patent family members

[redacted]onal Application No
PCT/CA 99/00005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4460599 A	17-07-1984	US 4268676 A	19-05-1981
		US 4885304 A	05-12-1989
		FR 2478101 A	18-09-1981
		FR 2477016 A	04-09-1981
		JP 56092288 A	25-07-1981
US 5169868 A	08-12-1992	AT 173459 T	15-12-1998
		AU 658611 B	27-04-1995
		AU 1323692 A	06-10-1992
		CA 2105171 A	02-09-1992
		WO 9215551 A	17-09-1992
		DE 69227627 D	24-12-1998
		DE 69227627 T	24-06-1999
		EP 0573498 A	15-12-1993
		JP 6505241 T	16-06-1994
		US 5508311 A	16-04-1996

COMPOSITION CONTAINING PROPARGYLAMINE FOR ENHANCING CANCER THERAPY

FIELD OF THE INVENTION

The present invention relates to a method for enhancing cancer therapy by administering an effective amount of an antineoplastic modulator. Preferred antineoplastic modulators are propargylamines including aliphatic propargylamines and aromatic propargylamines. The invention also includes a pharmaceutical composition for enhancing the treatment of cancer comprising an effective amount of an antineoplastic modulator of the present invention in admixture with a suitable diluent or carrier.

BACKGROUND OF THE INVENTION

Cancer is a collection of diseases involving inappropriate and unregulated growth of cells in the body. The aim of chemical therapy (chemotherapy) of cancer is to introduce a chemical (antineoplastic drug) which will kill the cancerous cells but will not damage normal cells. The early rationale for the development of conventional antineoplastic drugs was that such agents would act selectively on cells undergoing cell division; since cancerous cells were thought to be invariably dividing more rapidly than normal cells in the body, it was believed that this would offer some therapeutic selectivity. However, antineoplastic agents collectively have the lowest therapeutic indices of any class of drugs used in humans. This lack of selectivity leads to the severe side effects associated with cancer chemotherapy; the major dose-limiting consideration for use of these agents is toxicity to bone marrow. Furthermore, the poor selectivity of these agents means they must be used at sub-optimal doses. The latter, in turn, may cause the development of a variety of drug resistance traits by cancerous cells. Thus, many types of cancers are ultimately unresponsive to chemotherapy and are therefore incurable.

Notwithstanding such limitations, chemotherapy remains the only and thus the most important treatment option for disseminated

cancers. Despite decades of effort to find more effective and less toxic agents, the poor response of patients to conventional anticancer drugs and the limitations arising from intrinsic or acquired drug-resistance continue to limit the chemotherapeutic approach. It is estimated that over 50% of patients with advanced cancer will fail to respond, or will relapse from their initial response to chemotherapy, and will thus ultimately succumb to their disease. Given the prevalence and severity of disseminated disease, improving the chemotherapeutic treatment modality nevertheless remains a crucial objective of cancer research (1).

One novel and potentially major means of improving the chemotherapeutic modality of cancer treatment would be to improve the selectivity of the currently-available agents. To the degree to which selectivity could be improved, such an approach would diminish the toxic side effects and allow treatment with more appropriate doses of antineoplastics which, in turn, would diminish the inadvertent selection of drug-resistance variants during treatment. If, in addition, such a strategy would circumvent drug-resistance traits of either the intrinsic or acquired types, it would diminish all of the major, known limitations to conventional cancer chemotherapy. Remarkably, such an approach has been developed and verified to have all of these advantages in experimental chemotherapeutic models (2- 17). Termed the modulator approach for improving cancer chemotherapy, this novel strategy solves the major limitations otherwise associated with the use of conventional antineoplastics.

An antineoplastic modulator is a chemical which modifies the action of an antineoplastic drug, improving the selectivity, and therefore efficacy of the antineoplastic drug. An antineoplastic modulator acts, simultaneously, to advantage in three ways: i), it protects non-cancerous (normal) tissue from the toxic effects of the antineoplastic drug; ii), it increases the ability of the antineoplastic drug to kill cancerous cells, and iii), it suppresses the drug resistance traits exhibited by many cancerous cells.

The present inventors have prepared many novel propargylamines as described in United States Patent No. 5,169,868 and 5,840,979. The inventors have shown that the novel propargylamines are useful as MAO-B inhibitors and are useful in treating various neuropsychiatric disorders including Parkinson's disease, Alzheimer's disease, depression, attention deficit disorder, hyperactive disorders as well as other aging-associated diseases.

Surprisingly, the present inventors have found that the propargylamines are also useful as antineoplastic modulators and can enhance the effect of antineoplastic drugs.

SUMMARY OF THE INVENTION

Broadly stated, the present invention relates to a method of enhancing cancer therapy by administering an effective amount of a propargylamine. The present inventors have shown that propargylamines enhance the killing of tumor cells by antineoplastic drugs and protect normal cells from the cytotoxic effects of antineoplastic drugs. Consequently, propargylamines are well-suited to enhance any chemotherapy regime and can increase the effectiveness while reducing the side-effects of cancer therapy.

In one aspect, the present invention relates to a method for enhancing the effect of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

In another aspect, the present invention relates to a method of increasing the sensitivity of a tumor to an antineoplastic drug comprising administering an effective amount of propargylamine of the invention to an animal in need thereof.

In a further aspect, the present invention provides a method of protecting normal cells from the cytotoxic effects of an antineoplastic drug comprising administering an effective amount of a propargylamine of the invention to an animal in need thereof.

In a further aspect, the present invention relates to a method for treating cancer comprising administering an antineoplastic drug and

an effective amount of a propargylamine of the invention to an animal in need thereof.

The present invention also includes a use of a propargylamine of the present invention for the preparation of a medicament to be used in the therapeutic methods described herein.

The present invention further includes a pharmaceutical composition useful for enhancing cancer therapy comprising an effective amount of a propargylamine of the invention in admixture with a suitable diluent or carrier.

The pharmaceutical compositions of the present invention may be useful in (i) enhancing the activity of an antineoplastic drug, (ii) increasing the sensitivity of a tumor to an antineoplastic drug and/or (iii) protecting normal cells from the cytotoxic effects of an antineoplastic drug.

The present invention also includes a pharmaceutical composition useful for treating cancer comprising an antineoplastic drug and an effective amount of a propargylamine of the present invention.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in relation to the drawings in which:

Figure 1 is graph showing the RATIO of various antineoplastic modulators versus the concentration of the antineoplastic modulator. The definition of RATIO is provided in Example 1.

Figure 2 is a graph showing the relative cell survival of normal bone marrow versus time, in the presence of various modulators. HISOL=histindinol, cis=cisplatinum, 2HPA=R-2HPA.

Figure 3 is a graph showing the relative cell survival of cancer cells versus time, in the presence of various modulators.

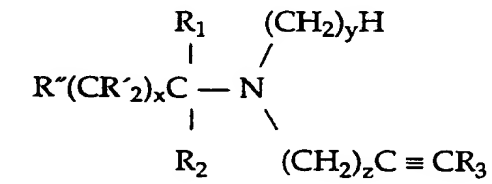
DETAILED DESCRIPTION OF THE INVENTION

Broadly stated, the present invention relates to a method of enhancing cancer therapy by administering an effective amount of a propargylamine. The present inventors have shown that propargylamines enhance the killing of tumor cells by antineoplastic drugs and protect normal cells from the cytotoxic effects of antineoplastic drugs. In addition, the propargylamines have been shown to overcome a drug-resistance attribute of tumor cells. *In vivo* data is included which verifies that these three powerful attributes of the approach are operative in live, tumor bearing animals. Consequently, propargylamines are well-suited to enhance any chemotherapy regime.

Propargylamines

The propargylamines that may be included in the methods, uses and compositions of the present invention include any propargylamine that can enhance the effect of an antineoplastic drug. The ability of a propargylamine to enhance the effect of an antineoplastic can be determined using the assays described in the Examples or using other assays known in the art.

In one embodiment, the propargylamine is of the general formula I



wherein

x is an integer ranging from 0 to 13;

y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R′ and R″ are the same or different and represent hydrogen, phenyl or a halogen and pharmaceutically acceptable salts thereof.

Preferably the lower alkyl has between 1 and 4 carbon atoms and the halogen atom is selected from fluorine, chlorine, bromine and iodine. More preferably, the lower alkyl is selected from methyl.

In another embodiment, the propargylamine is of the general formula I wherein y is 1 and the pharmaceutically acceptable salts thereof. A preferred propargylamine of the formula I wherein y is 1 is R-2-heptyl-methylpropargylamine (R-2HMP).

Other propargylamines of the formula I wherein y is 1 include:

N-(1-Propyl) N-methylpropargylamine;
N-(2-Propyl) N-methylpropargylamine;
N-(1-Butyl) N-methylpropargylamine;
N-(1-Pentyl) N-methylpropargylamine;
N-(1-Hexyl) N-methylpropargylamine;
N-(1-Heptyl) N-methylpropargylamine;
N-(1-Octyl) N-methylpropargylamine;
N-(1-Nonyl) N-methylpropargylamine;
N-(1-Decyl) N-methylpropargylamine;
N-(1-Undecyl) N-methylpropargylamine;
N-(1-Dodecyl) N-methylpropargylamine;
(R)-N-(2-Butyl) N-methylpropargylamine;
(R)-N-(2-Pentyl) N-methylpropargylamine;
(R)-N-(2-Hexyl) N-methylpropargylamine;
(R)-N-(2-Heptyl) N-methylpropargylamine;
(R)-N-(2-Octyl) N-methylpropargylamine;
(R)-N-(2-Octyl) N-methylpropargylamine;
(R)-N-(2-Decyl) N-methylpropargylamine;

(R)-N-(2-Undecyl) N-methylpropargylamine; and

(R)-N-(2-Dodecyl) N-methylpropargylamine.

In yet another embodiment, the propargylamine is of the general formula I, described above, wherein y is 0, and the pharmaceutically acceptable salts thereof. A preferred propargylamine of the formula I where y=0, is R-2-heptyl-propargylamine (R-2HPA).

Other compounds of the formula I, wherein y is 0, include:

N-(1-Propyl) propargylamine;

N-(2-Propyl) propargylamine;

N-(1-Butyl) propargylamine;

N-(1-Pentyl) propargylamine;

N-(1-Hexyl) propargylamine;

N-(1-Heptyl) propargylamine;

N-(1-Octyl) propargylamine;

N-(1-Nonyl) propargylamine;

N-(1-Decyl) propargylamine;

N-(1-Undecyl) propargylamine;

N-(1-Dodecyl) propargylamine;

(R)-N-(2-Butyl) propargylamine;

(R)-N-(2-Pentyl) propargylamine;

(R)-N-(2-Hexyl) propargylamine;

(R)-N-(2-Heptyl) propargylamine;

(R)-N-(2-Octyl) propargylamine;

(R)-N-(2-Octyl) propargylamine;

(R)-N-(2-Decyl) propargylamine;

(R)-N-(2-Undecyl) propargylamine; and

(R)-N-(2-Dodecyl) propargylamine.

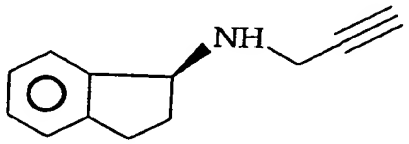
The preferred propargylamines of the chiral compounds of the formula I are the R-enantiomers.

In a further embodiment, the propargylamine is R-deprenyl. R-deprenyl is a compound of the formula I wherein R_1 is methyl, R_2 is

hydrogen, R˜ is phenyl, R´ is hydrogen, x is 1, y is 1, z is 1 and R_3 is hydrogen.

In another embodiment, the propargylamine is R-desmethyldeprenyl. R-desmethyldeprenyl is a compound of the formula I wherein R_1 is methyl, R_2 is hydrogen, R˜ is phenyl, R´ is hydrogen, x is 1, y is 0, z is 1 and R_3 is hydrogen.

In yet another embodiment, the propargylamine is Rasagiline having the following formula II:



All of the above described propargylamines may be collectively referred to as "the propargylamines of the invention".

The propargylamines of the present invention may be prepared using techniques known in the art. For example, the aliphatic propargylamines may be prepared as described in the inventors United States Patent No. 5,169,868 and 5,840,979 both which are incorporated herein by reference in their entirety. Briefly, the compounds may be prepared by condensing propargyl bromide with a chiral aliphatic amine or N-methylamine in the presence of a base and recovering the desired compound. Preferably the R-enantiomers are prepared.

Therapeutic Methods and Uses

As hereinbefore mentioned, the present invention relates to a method for enhancing the effect of an antineoplastic drug comprising administering an effective amount of a propargylamine of the invention to an animal in need thereof. The invention also includes a use of a propargylamine of the invention to enhance the effect of an antineoplastic drug.

The term "effective amount" as used herein means an amount effective, at dosages and for periods of time necessary to achieve the desired result.

The term "animal" as used herein means any member of the animal kingdom including all mammals, birds, fish, reptiles and amphibians. Preferably, the animal to be treated is a mammal, more preferably a human.

One method by which the propargylamines of the invention may enhance the effect of an antineoplastic drug is by increasing the sensitivity of the tumor to the drug. Accordingly, in one aspect, the present invention relates to a method of increasing the sensitivity of a tumor to an antineoplastic drug comprising administering an effective amount of propargylamine of the invention to an animal in need thereof. The tumor may be one that is resistant to cancer therapy such as a multidrug resistant tumor or a radioresistant tumor. This aspect also includes a use of a propargylamine of the invention to increase the sensitivity of a tumor to an antineoplastic agent.

Another method by which the propargylamines of the invention may enhance the effect of an antineoplastic drug is by protecting normal cells from the cytotoxic effects of the drug. Accordingly, in another aspect, the present invention provides a method of protecting normal cells from the cytotoxic effects of an antineoplastic drug comprising administering an effective amount of a propargylamine of the invention to an animal in need thereof. This aspect also includes a use of a propargylamine of the invention to protect normal cells from the cytotoxic effects of an antineoplastic drug.

In a further aspect, the present invention relates to a method for treating cancer comprising administering an antineoplastic drug and an effective amount of a propargylamine of the invention to an animal in need thereof. This aspect includes a use of (a) a propargylamine and (b) an antineoplastic drug to treat cancer.

The propargylamines of the invention can be used to enhance the treatment of all forms of cancer or malignant diseases for which chemotherapy is a bona fide treatment option. These malignancies include, but are not limited to, leukemias, lymphomas (Hodgkins and

non-Hodgkins), plasmacytomas, histiocytomas, melanomas, adenomas, sarcomas, carcinomas of solid tissues, hypoxic tumours, squamous cell carcinomas, genitourinary cancers such as cervical and bladder cancer, hematopoietic cancers, head and neck cancers, and nervous system cancers. Treatment with the propargylamine modulators may allow for treatment of tumors that are resistant to chemotherapy. The latter are diverse, but one common, well-studied example is the so-called multi-drug resistant (MDR) tumor cells. MDR tumors include adenocarcinomas, neuroblastoma cells, leukemias, lymphomas, breast cancer and ovarian cancer cells. Treatment with the propargylamine modulators may also allow for more effective radiotherapy of tumours that currently respond poorly to radiotherapy such as adenocarcinomas of the bowel and lung.

Antineoplastic drugs which may be potentiated or enhanced by the propargylamine modulators can be any antineoplastic drug including known, conventional drugs as well as those yet to be identified. Examples of classes of antineoplastic agents include antimetabolites, alkylating agents, antimicrobial antineoplastics, antimicrotubule agents, cisplatinum and its derivatives and the topoisomerase interactive agents. In particular, chemotherapeutic agents amenable to this modulatory effect may include but are not limited to, adriamycin, BCNU and CCNU (i.e., bis (2-chloroethyl)-3-cyclohexyl-1-nitrosurea and 1-(2-chloroethyl)-3-cyclohexyl -1-nitrosourea, respectively, bleomycin sulfate, camptothecin, carmustine, chlorambucil, cisplatinum, cyclophospamide, cytosine arabinoside, daunomycin/daunorubicin, dacarbazine, doxorubicin, 5-fluorouracil, melphalan, mitomycin, mitoxantrone hydrochloride, etoposide, streptozocin and taxol and taxol derivatives.

Although the propargylamines of the invention may be administered before, after and/or concurrently with the antineoplastic drug, they are likely best administered prior to chemotherapy.

Pharmaceutical Compositions

The propargylamines of the invention may be incorporated into a pharmaceutical composition which may be useful in enhancing the activity of an antineoplastic drug, increasing the sensitivity of a tumor to an antineoplastic drug and/or protecting normal cells from the cytotoxic effects of an antineoplastic drug. The pharmaceutical composition may additionally include an antineoplastic drug and may be useful for treating cancer.

The pharmaceutical compositions of the invention can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to patients, and such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985). The pharmaceutical compositions of the invention can be for oral, topical, rectal, parenteral, local, intravenous, inhalant or intracerebral use. They may be in solid or semisolid form, for example pills, tablets, creams, gelatin capsules, capsules, suppositories, soft gelatin capsules, gels, membranes, tubelets. For parenteral and intracerebral uses, those forms for intramuscular or subcutaneous administration can be used, or forms for infusion or intravenous or intracerebral injection can be used, and can therefore be prepared as solutions of the active compounds or as powders of the active compounds to be mixed with one or more pharmaceutically acceptable excipients or diluents, suitable for the aforesaid uses and with an osmolarity which is compatible with the physiological fluids. For local use, those preparations in the form of creams or ointments for topical use or in the form of sprays should be considered; for inhalant uses, preparations in the form of sprays, for example nose sprays, should be considered. Dosages to be administered depend on individual needs, on the desired effect and on the chosen route of administration, but daily dosages to humans by subcutaneous,

intramuscular, intravenous or intracerebral injection generally vary between about 100 ng and 100 µg of active substance per Kg body weight, preferably between 1 µg and 50 µg per Kg body weight for the aliphatic propargylamines. For aromatic propargylamines, the above doses may be increased ten fold.

The following non-limiting examples are illustrative of the present invention:

EXAMPLES

EXAMPLE 1

***In Vitro* Protocol for Assessing the Capacity of Various Compounds to Modulate Cisplatinum Toxicity**

The protocol detailed below can be used for any normal/tumorigenic cell pair which will attach to plastic. Non-adherent lines (which includes most tumor cells, including NW16; consult references 5-10) require quantitation in soft agar. The present experiments are based on i) rat2 cells, a phenotypically normal, established rat fibroblast line and, ii) a tumorigenic derivative thereof, NW16 cells, which are rat2 cells transformed by a Fujinami sarcoma virus oncogene (see work of A. Pawson and $P130^{gag\text{-}fps}$). Rat2 and NW16 cells are maintained in a sub-confluent randomly-proliferating state in Dulbecco's modified minimal essential media with 10% (vol/vol) calf serum in plates incubated at 37°C in a humidified CO_2 (10%) incubator. All experiments reported rely on clonogenic cell survival assays (see references 4-6). Assays using rat2 (normal cells) were performed as follows: cells are exposed, in 10 cm culture dishes, to various drugs in media plus serum for varying lengths of time; seeding is at varying cell numbers, over $\log_{10}$ ranges, depending upon the degree of killing anticipated. [For the figure presented, incubation was for 72 hours prior to washing and assessment of clonogenic survival]. Both control and the experimental cultures are then gently washed, twice, with phosphate buffered saline, then once more with media minus serum, and then left in media plus serum, undisturbed until macroscopic colonies appear (7-9 days of incubation). The colonies are

then fixed and stained with saturated methylene blue in 50% methanol and counted. The number of colonies, evaluated from 2 or more sets of duplicate cultures seeded at initial densities differing by factors of 10, are determined and converted to relative number of colonies, using the 0-hour control value as 1.0. Assays of NW16 cells were similar; however, because these cells are poorly adherent, following drug exposure, the washing procedure is modified, as is the quantitation of survivors step. In the latter case, quantitation requires plating the cells in soft agar (references 5-10).

Presentation of Results by "RATIO" Method

A simplified presentation of the data, by the RATIO method, is show in Figure 1. By dividing the relative cell survival (R.C.S.) value obtained in cultures which have been exposed to the combination of anticancer drug (in this case, cisplatinum) and modulator by the corresponding R.C.S. value obtained for the anticancer drug alone reveals both the nature and the magnitude of the effect mediated by the modulator. Ratios greater than unity indicate that the modulator has conferred a protective response, whereas ratios less than unity indicate an enhanced cell killing.

Results

As can be seen from Figure 1, R-2-heptyl-propargylamine (R-2HPA), the desmethyl metabolite of R-2-heptyl-methyl propargylamine (R-2HMP), and R-2HMP (the pro-drug) are effective, over a wide concentration range (10^{7} - 10^{-15} M), at protecting normal fibroblasts which are p53 dependent. R-2HPA is the more potent. R-Deprenyl whilst active, is less efficacious over a more limited concentration range (10^{-7} - 10^{-13} M). The usually inactive pro-drug isomer S-2HMP is also inactive in this assay. In the tumorigenic cells (mutants in which p53 is absent) it can be seen that enhanced killing by cisplatinum occurs in the range (10^{-11} - 10^{-15} M) but with a reversal to a protective effect when the concentration of R-2HMP is 10^{-9}M or greater.

Summary

R-2HMP and R-2HPA both protect normal cells and enhance the killing of tumor cells in the presence of cisplatinum in this *in vitro* fibroblast model. The protection and the enhanced killing occur in the 10^{-11} - 10^{-15} M range. R-Deprenyl was also effective over a more limited concentration, in the 10^{-7} to 10^{-13} M range. Since L-histidinol exhibits similar properties (although higher doses are required) in this and several other *in vitro* and *in vivo* paradigms, and in the presence of other anticancer drugs, it is reasonable to predict that R-2HMP, R-2HPA and the other aliphatic propargylamines, by analogy, will also exhibit activity in these other systems.

EXAMPLE 2

***In Vivo* Assessment of Anticancer Drug Modulators: Effects of R-2HPA**

Seven groups of mice were treated and assessed in this model as follows:

1. Nil control (1 mouse)
2. P388 control (1 mouse)
3. Cisplatinum (5 mice)
4. Histidinol (2 mice)
5. Histidinol + cisplatinum (5 mice)
6. R-2HPA (4 mice)
7. R-2HPA + cisplatinum (5 mice)

P388 cells (1 million) were injected into the tail vein of 22 female DBA/2J mice (Protocol first developed in reference 6 and 8). The mice were then randomly divided into the above groups and injected (ip) with drugs 96h later. Doses were cisplatinum 0.2 mg at 0 hour; Histidinol 5 mg/injection and R-2HPA 0.38 ug/injection; administered 5 times at -2, 0, +2, +4, and +6 hours. 48 h after drug treatment, cells from the femurs of the mice were harvested, washed and plated (at log10 dilutions) so as to allow quantitative and specific relative cell survival values to be generated for the responses of normal femoral bone marrow cells (specifically,

CFU-C/GM or granulocyte/macrophage precursor cells) and clonogenic P388 leukemia cells (8).

As can be seen in Figure 2, both histidinol and R-2HPA were effective at protecting normal bone marrow cells, whereas in Figure 3, it can be seen that both histidinol and R-2HPA enhanced the killing by cisplatinum of P388 cells. It should be emphasized that the P388 leukemic line is substantially resistant to the cisplatinum (relative to the responses of the CFU-c/GM cells). This is an example of the poor therapeutic index common to conventional antineoplastics. In this example, the cisplatinum, when used alone, can be seen to be about 100-times more effective at killing the crucial normal marrow cells than it is for killing the intrafemoral leukemia (tumor) cells. In the presence of the modulators histidinol and R-2HPA, the therapeutic index of cisplatinum is vastly improved; thus, the toxicity to the marrow cells is essentially eliminated and the toxicity to the leukemia cells is increased by almost a 1000-fold. In other words, both histidinol and R-2HPA are simultaneously protecting the most vulnerable normal cells from cancer drug toxicity and simultaneously circumventing a profound drug-resistance trait. That these effects are observed *in vivo* (i.e., in live animals) and in the same tissue of those animals cannot be over-emphasized in terms of its potential capacity to improve chemotherapy, in as much as it reveals clearly and dramatically the ability of modulators to improve selectivity, efficacy and to circumvent the problem of drug-resistance shown by tumor cells. It can also be seen that this remarkable effect is obtained with R-2HPA at the low dose of 0.38 ug, producing a therapeutic index of about 50,000 between the protection of healthy normal cells and the killing of the cancerous cells. This effect is known to be p53 dependent vis a vis histidinol and it is likely to be the same with R-2HPA.

The modulator strategy has been shown to be remarkably effective in many *in vivo* tumor models (4-6; 7-11), in numerous types of human cancer cells (12,13) and in many kinds of drug resistance traits (5; 16,17). Consequently, considering the data cited herein, it is predicted that

the use of propargylamines as antineoplastic modulators will improve the chemotherapeutic management of a wide variety of human malignant disease types which will include non-resistant, intrinsic and acquired drug-resistance types. The modulator approach has been validated experimentally to markedly improve treatment of malignancies of myeloid origin (leukemias, lymphomas, and cancers of "blood cell" origin; (7-10) and for disseminated or metastatic disease (11); these are the situations wherein chemotherapy is often the only available clinical treatment option, the least responsive to treatment and/or the most prone to failure due to either intrinic or acquired drug-resistance and hence incurable status.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

FULL CITATIONS FOR REFERENCES REFERRED TO IN THE SPECIFICATION

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12) R C Warrington, I Cheng, L Zhang and WD Fang, 1993. L-Histidinol increases the vulnerability of cultured human leukemia and lymphoma cells to anticancer drugs. *Anticancer Res. 13:* 2107-2112.

13) RC Warrington, I Cheng and W D Fang, 1994. Susceptibility of human colon carcinoma cells to anticancer drugs is enhanced by L-histidinol. *Anticancer Research, 14 :* 367-372.

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15) RC Warrington, WD Fang, L Zhang, M Shieh and MH Saier, 1996. Mimetics of L-histidinol which selectively modulate daunomycin toxicity in normal and tumorigenic epithelial cells. *Anticancer Res. 16:* 3635-3640.

16) RC Warrington and W.D. Fang, 1989. Reversal of the Multidrug-Resistant Phenotype of Chinese Hamster Ovary Cells by L-histidinol. *Journal of the National Cancer Institute, 81,* 798-803

17) RC Warrington, WD Fang and L Zhang, 1996. L-Histidinol reverses resistance of cisplatinum and other antineoplastics in a tumorigenic epithelial cell line. *Anticancer Res. 16:* 3641-3645.

WE CLAIM:

1. A use of a propargylamine to enhance the activity of an antineoplastic drug.

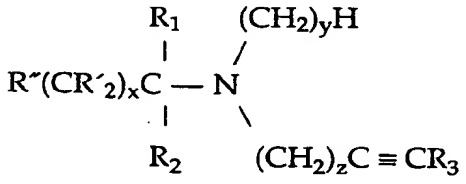
2. A use according to claim 1 wherein the propargylamine increases the sensitivity of a tumor to the antineoplastic drug.

3. A use according to claim 2 wherein the tumor is a drug resistant tumor.

4. A use according to claim 1 wherein the propargylamine protects normal cells from the cytotoxic effects of the antineoplastic drug.

5. A use of (a) a propargylamine and (b) an antineoplastic drug to treat cancer.

6. A use according to any one of claims 1-5 wherein the propargylamine is of the general formula I



wherein

x is an integer ranging from 0 to 13;

y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R´ and R˝ are the same or different and represent hydrogen, phenyl or a halogen and pharmaceutically acceptable salts thereof.

7. A use according to claim 6 wherein y is 1.

8. A use according to claim 7 wherein the propargylamine is R-2-heptyl-methyl propargylamine (R-2HMP).

9. A use according to claim 7 wherein the propargylamine is selected from the group consisting of N-(1-Propyl) N-methylpropargylamine; N-(2-Propyl) N-methylpropargylamine; N-(1-Butyl) N-methylpropargylamine; N-(1-Pentyl) N-methylpropargylamine; N-(1-Hexyl) N-methylpropargylamine; N-(1-Heptyl) N-methylpropargylamine; N-(1-Octyl) N-methylpropargylamine; N-(1-Nonyl) N-methylpropargylamine; N-(1-Decyl) N-methylpropargylamine; N-(1-Undecyl) N-methylpropargylamine; N-(1-Dodecyl) N-methylpropargylamine; (R)-N-(2-Butyl) N-methylpropargylamine;(R)-N-(2-Pentyl) N-methylpropargylamine;(R)-N-(2-Hexyl) N-methylpropargylamine; (R)-N-(2-Heptyl) N-methylpropargylamine;(R)-N-(2-Octyl) N-methylpropargylamine; (R)-N-(2-Octyl) N-methylpropargylamine; (R)-N-(2-Decyl) N-methylpropargylamine; (R)-N-(2-Undecyl) N-methylpropargylamine; and (R)-N-(2-Dodecyl) N-methylpropargylamine.

10. A use according to claim 6 wherein y is 0.

11. A use according to claim 10 wherein the propargylamine is R-2-heptyl-propargylamine (R-2HPA).

12. A use according to claim 10 wherein said propargylamine is selected from the group consisting of N-(1-Propyl) propargylamine; N-(2-Propyl) propargylamine; N-(1-Butyl) propargylamine; N-(1-Pentyl) propargylamine; N-(1-Hexyl) propargylamine; N-(1-Heptyl) propargylamine; N-(1-Octyl) propargylamine; N-(1-Nonyl)

propargylamine; N-(1-Decyl) propargylamine; N-(1-Undecyl) propargylamine; N-(1-Dodecyl) propargylamine; (R)-N-(2-Butyl) propargylamine; (R)-N-(2-Pentyl) propargylamine; (R)-N-(2-Hexyl) propargylamine; (R)-N-(2-Heptyl) propargylamine; (R)-N-(2-Octyl) propargylamine; (R)-N-(2-Octyl) propargylamine; (R)-N-(2-Decyl) propargylamine; (R)-N-(2-Undecyl) propargylamine; and (R)-N-(2-Dodecyl) propargylamine.

13. A use according to any one of claims 1 to 7, 9, 10 or 12 wherein the propargylamine is a chiral compound and is the R-enantiomer.

14. A use according to any one of claims 1-6 wherein the propargylamine is R-deprenyl.

15. A use according to any one of claims 1-6 wherein the propargylamine is R-desmethyldeprenyl.

16. A use according to any one of claims 1-5 wherein the propargylamine is Rasagiline.

17. A use according to any one of claims 1-16 wherein the animal is a human.

18. A use according to any one of claims 1-17 wherein the antineoplastic drug is selected from the group consisting of cytosine arabinoside, cis-platinum, cyclophospamide, adriamycin, daunomycin, and 5-fluorouracil.

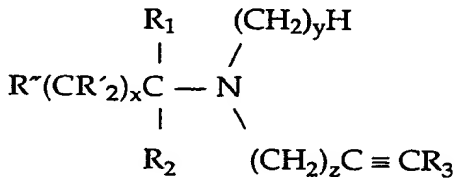
19. A pharmaceutical composition for enhancing the activity of an antineoplastic drug comprising an effective amount of a propargylamine in admixture with a suitable diluent or carrier.

20. A pharmaceutical composition according to claim 19 for increasing the sensitivity of a tumor to the antineoplastic drug.

21. A pharmaceutical composition according to claim 19 for protecting normal cells from the cytotoxic effects of the antineoplastic drug.

22. A pharmaceutical composition for treating cancer comprising an antineoplastic drug and an effective amount of a propargylamine.

23. A pharmaceutical composition according to any one of claims 19 to 22, wherein the propargylamine is of the general formula I:



wherein

x is an integer ranging from 0 to 13;

y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R′ and R″ are the same or different and represent hydrogen, phenyl or a halogen and pharmaceutically acceptable salts thereof.

24. A pharmaceutical composition according to claim 23 wherein y is 1.

25. A pharmaceutical composition according to claim 24 wherein the propargylamine is R-2-heptyl-methyl propargylamine (R-2HMP).

26. A pharmaceutical composition according to claim 24 wherein the propargylamine is selected from the group consisting of N-(1-Propyl) N-methylpropargylamine; N-(2-Propyl) N-methylpropargylamine; N-(1-Butyl) N-methylpropargylamine; N-(1-Pentyl) N-methylpropargylamine; N-(1-Hexyl) N-methylpropargylamine; N-(1-Heptyl) N-methylpropargylamine; N-(1-Octyl) N-methylpropargylamine; N-(1-Nonyl) N-methylpropargylamine; N-(1-Decyl) N-methylpropargylamine; N-(1-Undecyl) N-methylpropargylamine; N-(1-Dodecyl) N-methylpropargylamine; (R)-N-(2-Butyl) N-methylpropargylamine; (R)-N-(2-Pentyl) N-methylpropargylamine; (R)-N-(2-Hexyl) N-methylpropargylamine; (R)-N-(2-Heptyl) N-methylpropargylamine; (R)-N-(2-Octyl) N-methylpropargylamine; (R)-N-(2-Octyl) N-methylpropargylamine; (R)-N-(2-Decyl) N-methylpropargylamine; (R)-N-(2-Undecyl) N-methylpropargylamine; and (R)-N-(2-Dodecyl) N-methylpropargylamine.

27. A pharmaceutical composition according to claim 23, wherein y is 0.

28. A pharmaceutical composition according to claim 27 wherein the propargylamine is R-2-heptyl-propargylamine (R-2HPA).

29. A pharmaceutical composition according to claim 27 wherein said propargylamine is selected from the group consisting of N-(1-Propyl) propargylamine; N-(2-Propyl) propargylamine; N-(1-Butyl) propargylamine; N-(1-Pentyl) propargylamine; N-(1-Hexyl) propargylamine; N-(1-Heptyl) propargylamine; N-(1-Octyl) propargylamine; N-(1-Nonyl) propargylamine; N-(1-Decyl) propargylamine; N-(1-Undecyl) propargylamine; N-(1-Dodecyl) propargylamine; (R)-N-(2-Butyl) propargylamine; (R)-N-(2-Pentyl) propargylamine; (R)-N-(2-Hexyl) propargylamine; (R)-N-(2-Heptyl)

propargylamine; (R)-N-(2-Octyl) propargylamine; (R)-N-(2-Octyl) propargylamine; (R)-N-(2-Decyl) propargylamine; (R)-N-(2-Undecyl) propargylamine; and (R)-N-(2-Dodecyl) propargylamine.

30. A pharmaceutical composition according to any one of claims 19 to 24, 26, 27 or 29 wherein the propargylamine is a chiral compound and is the R-enantiomer.

31. A pharmaceutical composition according to any one of claims 19 to 23, wherein the propargylamine is R-deprenyl.

32. A pharmaceutical composition according to any one of claims 19 to 23, wherein the propargylamine is R-desmethyldeprenyl.

33. A pharmaceutical composition according to any one of claims 19 to 22, wherein the propargylamine is Rasagiline.

34. A method for enhancing the activity of an antineoplastic drug comprising administering an effective amount of a propargylamine to an animal in need thereof.

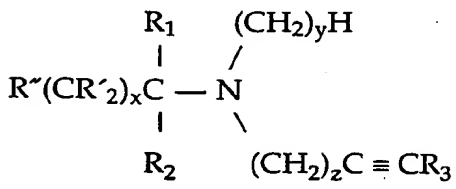
35. A method according to claim 34 wherein the propargylamine increases the sensitivity of a tumor to an antineoplastic drug.

36. A method according to claim 35 wherein the tumor is a drug resistant tumor.

37. A method according to claim 34 wherein the propargylamine protects normal cells form the cytotoxic effects of the antineoplastic drug.

38. A method for treating cancer comprising administering an antineoplastic drug and an effective amount of a propargylamine to an animal in need thereof.

39. A method according to any one of claims 34 to 38, wherein the propargylamine is of the general formula I



wherein

x is an integer ranging from 0 to 13;

y is an integer ranging from 0 to 5;

z is an integer ranging from 0 to 5;

R_1, R_2 and R_3 are the same or different and represent hydrogen or a straight chain or branched lower alkyl; and

R′ and R″ are the same or different and represent hydrogen, phenyl or a halogen and pharmaceutically acceptable salts thereof.

40. A method according to claim 39 wherein y is 1.

41. A method according to claim 40 wherein the propargylamine is R-2-heptyl-methyl propargylamine (R-2HMP).

42. A method according to claim 39 wherein the propargylamine is selected from the group consisting of N-(1-Propyl) N-methylpropargylamine; N-(2-Propyl) N-methylpropargylamine; N-(1-Butyl) N-methylpropargylamine; N-(1-Pentyl) N-methylpropargylamine; N-(1-Hexyl) N-methylpropargylamine; N-(1-Heptyl) N-methylpropargylamine; N-(1-Octyl)

N-methylpropargylamine; N-(1-Nonyl) N-methylpropargylamine; N-(1-Decyl) N-methylpropargylamine; N-(1-Undecyl) N-methylpropargylamine; N-(1-Dodecyl) N-methylpropargylamine; (R)-N-(2-Butyl) N-methylpropargylamine; (R)-N-(2-Pentyl) N-methylpropargylamine; (R)-N-(2-Hexyl) N-methylpropargylamine; (R)-N-(2-Heptyl) N-methylpropargylamine; (R)-N-(2-Octyl) N-methylpropargylamine; (R)-N-(2-Octyl) N-methylpropargylamine; (R)-N-(2-Decyl) N-methylpropargylamine; (R)-N-(2-Undecyl) N-methylpropargylamine; and (R)-N-(2-Dodecyl) N-methylpropargylamine.

43. A method according to claim 39, wherein y is 0.

44. A method according to claim 43 wherein the propargylamine is R-2-heptyl-propargylamine (R-2 HPA).

45. A method according to claim 43 wherein the propargylamine is selected from the group consisting of N-(1-Propyl) propargylamine; N-(2-Propyl) propargylamine; N-(1-Butyl) propargylamine; N-(1-Pentyl) propargylamine; N-(1-Hexyl) propargylamine; N-(1-Heptyl) propargylamine; N-(1-Octyl) propargylamine; N-(1-Nonyl) propargylamine; N-(1-Decyl) propargylamine; N-(1-Undecyl) propargylamine; N-(1-Dodecyl) propargylamine; (R)-N-(2-Butyl) propargylamine; (R)-N-(2-Pentyl) propargylamine; (R)-N-(2-Hexyl) propargylamine; (R)-N-(2-Heptyl) propargylamine; (R)-N-(2-Octyl) propargylamine; (R)-N-(2-Octyl) propargylamine; (R)-N-(2-Decyl) propargylamine; (R)-N-(2-Undecyl) propargylamine; and (R)-N-(2-Dodecyl) propargylamine.

46. A method according to any one of claims 34 to 39, wherein the propargylamine is R-deprenyl.

47. A method according to any one of claims 34 to 39, wherein the propargylamine is R-desmethyldeprenyl.

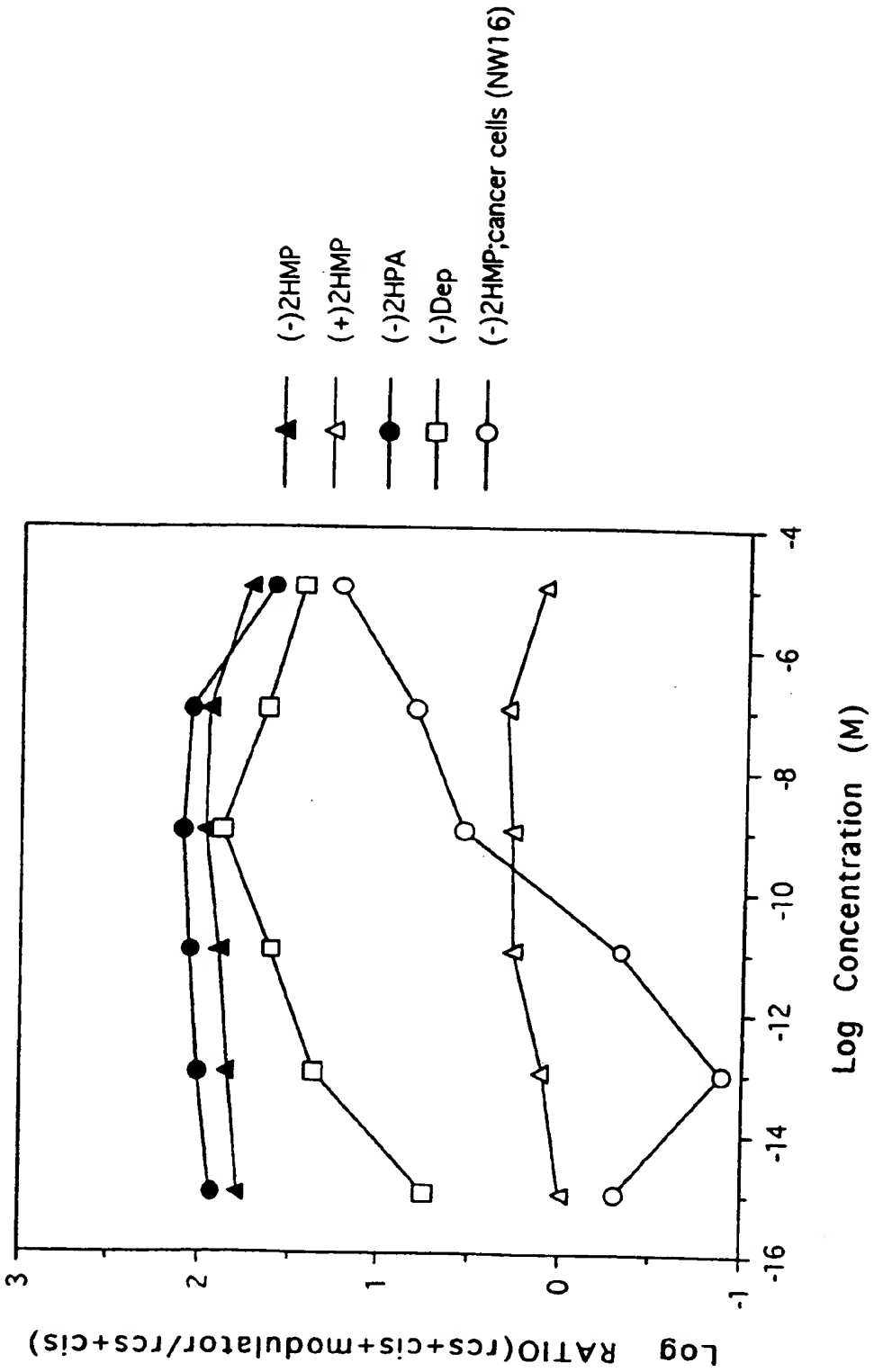
48. A method according to any one of claims 34 to 38, wherein the propargylamine is Rasagiline.

49. A method according to any one of claims 34 to 48, wherein the animal is a human.

50. A method according to any one of claims 34 to 49 wherein the antineoplastic drug is selected from the group consisting of cytosine arabinoside, cis-platinum, cyclophospamide, adriamycin, daunomycin, and 5-fluorouracil.

51. A method according to any one of claims 34 to 40, 42, 43 and 45 wherein the propargylamine is a chiral compound and is the R-enantiomer.

FIGURE 1


(-)2HMP
(+)2HMP
(-)2HPA
(-)Dep
(-)2HMP;cancer cells (NW16)
Log RATIO(rcs+cis+modulator/rcs+cis)
3
2
1
0
-1
-4
-6
-8
-10
-12
-14
-16
Log Concentration (M)

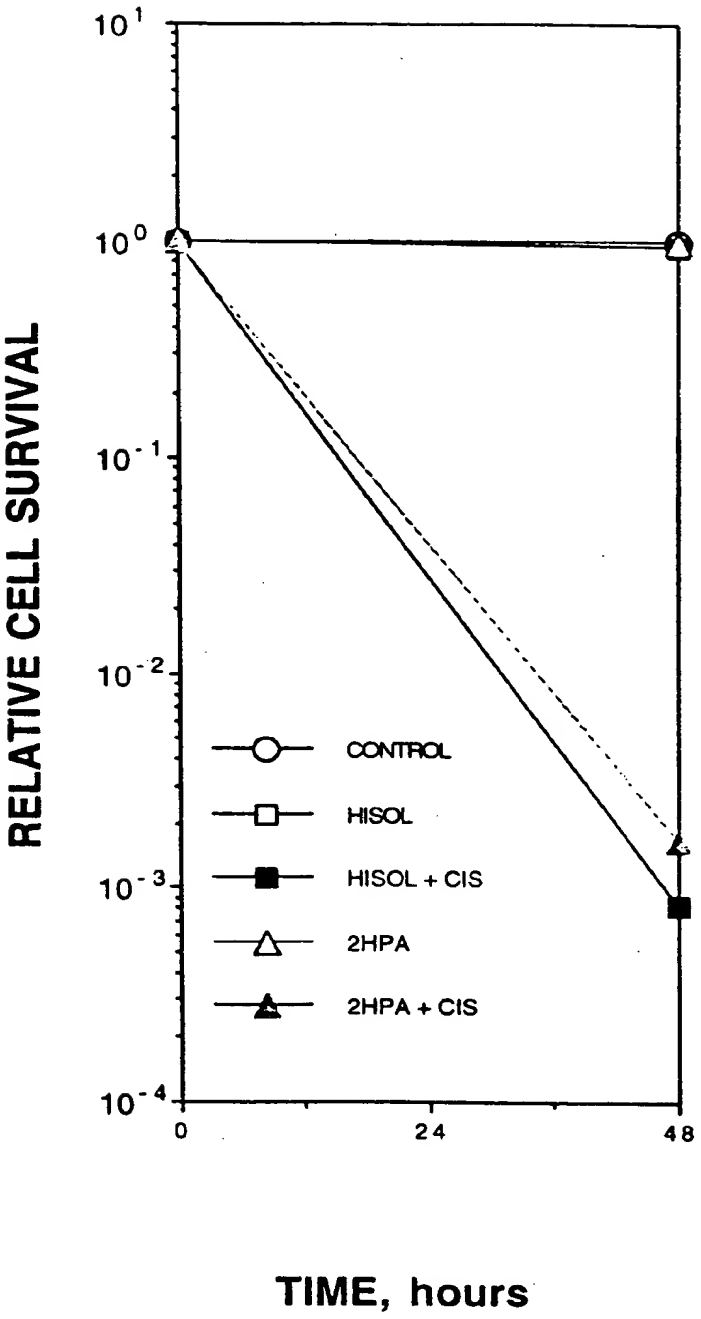

RELATIVE CELL SURVIVAL
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
24
48
CONTROL
HISOL
HISOL + CIS
2HPA
2HPA + CIS
TIME, hours

FIGURE 2

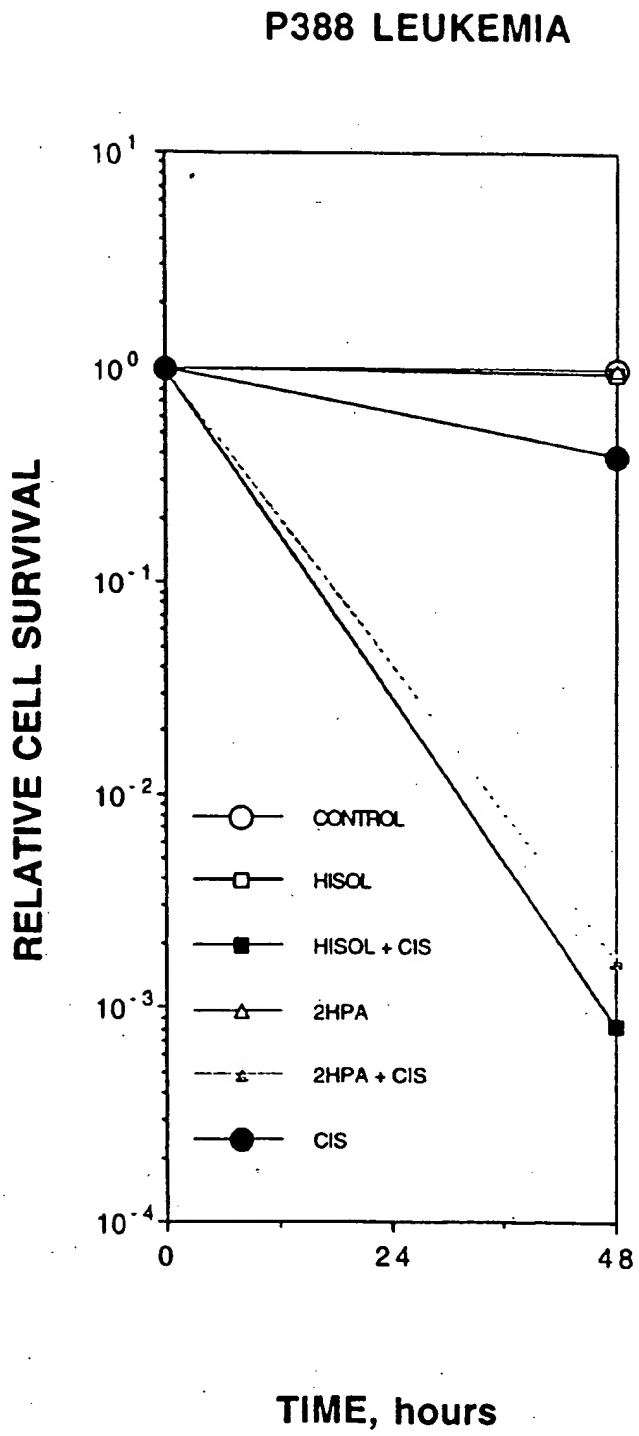

P388 LEUKEMIA
RELATIVE CELL SURVIVAL
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
24
48
CONTROL
HISOL
HISOL + CIS
2HPA
2HPA + CIS
CIS
TIME, hours

FIGURE 3